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(54) Composition useful in the treatment of estrogen deficiencies.

(57) Medication and pharmaceutical composition containing at least one synthetic estrogenic compound and at least one progestogenic compound for the treatment of estrogen deficiency.

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Description

COMPOSITIONS USEFUL IN THE TREATMENT OF ESTROGEN DEFICIENCIES

The treatment of menopausal symptoms such as osteoporosis and other ailments associated with estrogen deficiency is old. Typically, the known formulations for such treatment have contained natural estrogen or other estrogenic component(s) as the only hormonal ingredient. The replacement of estrogen with these types of formulations containing estrogen only, has led to evidence of adenocarcinoma of the endometrium.

The use of natural progesterone or other progestogenic agents along with estrogenic substances has been found to reduce various undesirable side effects associated with the use of estrogen agents alone.

Applicant has discovered that a fixed combination of estrogenic and progestogenic agents gives relief from menopausal symptoms with minimal side effects. In one preferred embodiment, a composition containing a fixed dosage of ethinyl estradiol,--i.e., 0.005-0.05 mg--along with a fixed dosage of norethindrone acetate--i.e., 0.1-1.0 mg--yields, when administered as a daily dosis in a 28-day sequence, gives acceptable estrogen levels in patients.

Thus, the invention is concerned with compositions and methods in which a formulation containing a fixed estrogen/progestin ratio is administered to female individuals with resultant relief from osteoporosis and other conditions associated with estrogen deficiency.

The compositions and processes of the invention have several advantages over those already known in the art. Principal among their advantages are:

The compositions contain fixed, i.e., constant or unitary, quantities of both the estrogenic and progestogenic agents. This simplifies manufacturing, storage and packaging.

The use of a continuously dosed product minimizes patient compliance problems

The administration of a single combination product containing fixed quantities of hormonal agents psychologically beneficial. Also it has been demonstrated that low doses of this combination of hormones frequently results in an amenorrheic state that obviates the troublesome side effect of monthly withdrawal bleeding.

Other aspects and advantages of the invention will be made apparent by the following description and claims. The present invention refers to a medication, characterized in that it is composed of at least one synthetic estrogenic compound and at least one progestogenic compound.

It further refers to a pharmaceutical composition, characterized in that it comprises as active principles at least one synthetic estrogenic compound and at least one progestogenic compound.

The present invention further refers to a method of use of a combination of at least one estrogenic compound and at least one progestogenic compound for the manufacture of a medication or a pharmaceutical composition as described herein, especially for the treatment of estrogen deficiency, especially for the treatment of osteoporosis.

The present invention further includes a method of preparation of a medication or a pharmaceutical preparation as described herein, characterized in that at least one estrogenic compound and at least one progestogenic compound are synergistically combined into a medication or a pharmaceutical preparation according to this invention.

The compositions (medications and pharmaceutical compositions) and methods of the invention are based upon the use of a novel combination of synthetic estrogenic and progestogenic ingredients.

The compositions generally contain about 0.001 to about 0.1 parts by weight, preferably about 0.005 to about 0.05 parts of the estrogenic ingredient and about 0.1 to about 2.0 parts by weight, and preferably about 0.1 to about 1.0 parts by weight of the progestogenic ingredient.

Generally, the ratios by weight of estrogenic to progestogenic components in the inventive compositions will be from about 0.005:1 to about 1:1, preferably about 0.005:1 to about 0.02:1.

While milligrams are the preferred units of measurement, any scale can be used so long as the ratio of the active hormonal ingredients remains fixed and is appropriate to the weight ratios set out above.

The estrogenic ingredient of the inventive compositions can be any suitable synthetic estrogen or functional equivalent thereof. While ethinyl estradiol is the preferred estrogenic substance, other useful substances include conjugated estrogens, estrone sulfate, beta estradiol, quinestrol, and the like. Mixtures are operable.

The progestogenic ingredient is generally a synthetic progestogen; however, natural progestins may be used. Useful progestogenic substances include medroxy-progesterone acetate and the like. Norethindrone acetate is preferred. Mixtures are operable.

While it is preferred that the synthetic estrogen and progestin be the only pharmaceutically active ingredients in the compositions, the use of other drugs and/or otherwise beneficial substances in the instant compositions is contemplated.

The use of conventional pharmaceutical carriers is contemplated. Other excipients such as perfumes, colorants, stabilizers fillers, and the like can be used as well.

The compositions of the invention can be administrated via a variety of routes. Any method of combination of methods by which a continuous dosage form can be administered is operable. Oral dosage forms are preferred.

When oral dosage forms are employed, it is generally preferred that they be solid or semisolid. However, liquid compositions are contemplated.

One aspect of the invention involves the packaging of the compositions of the invention, in a solid dosage form, in a pill case or compact for sequential administration. Thus, a package similar to that sometimes used for dispensing contraceptive pills, tablets, and the like can be employed. Thus, the individual who is to ingest the subject composition merely takes the pills, tablets, and/or capsule in a daily regimen in the sequence in which they are presented in the package.

In general, any dosage form and packaging concept can be used in combination so long as the composition is administered at least once daily for a period of about 20 to about 30 days, preferably about 28 days, during a total cycle of about 30 to about 35 days. One highly preferred regimen calls for continuous administration of the composition to a human female for about 28 days of an approximately 30-day cycle.

The compositions of the invention are useful for treating osteoporosis, withdrawal bleeding, and other disorders and symptoms generally associated with estrogen deficiency, many of which are experienced during menopause.

The invention is illustrated by the following example(s).

Example 1

1.00g ethinyl estradiol U.S.P., (0.5% dilution (=0.005 g dry substance), 5% excess) was combined with 0.5 g norethindrone acetate USP. 8.66g Hydrous Fast Flo lactose U.S.P. and 7.00g corn starch N.F. (National Formulary) in a suitable liquids/solids PK blender equipped with intensifier bar. The ingredients were blended for five minutes. All mixing was done using the intensifier bar unless specified otherwise.

17.50g microcrystalline cellulose NF Powder was added to the resultant blend and mixed for 5 minutes. 34.64g Hydrous Fast Flo lactose U.S.P. was added and all ingredients were blended for 5 minutes.

Thereafter, 0.70g calcium stearate NF powder was added and blended with the intensifier bar for 1 minute and without it for 1 minute.

The final mixture was compressed 70 mg on 7/32 FFBE punches at 4-6 kg hardness and about 0.085" gauge. One thousand tablets were produced from the composition.

Examples 2-4

Using the same procedure described above, tablets were produced using the following ingredients:

Ingredient	Quantity (grams)		
	Ex. 2	Ex. 3	Ex. 4
Ethinyl estradiol, USP (0.5% dilution, w/5% excess)	2.00	1.00	2.00
Norethindrone acetate, USP	0.50	1.00	1.00
Lactose, Hydrous Fast Flo, USP			
Initial Quantity:	8.46	8.56	8.36
Added Quantity:	33.84	34.24	33.44
Corn Starch, NF	7.00	7.00	7.00
Microcrystalline cellulose	17.50	17.50	17.50
Calcium stearate	0.70	0.70	0.70

Reasonable variations, such as those which would occur to a skilled artisan, can be made herein without departing from the scope of the invention.

Claims

1. Medication, characterized in that it is composed of at least one syntetic estrogenic compound and at least one progestogenic compound.

2. A pharmaceutical composition, characterized in that it comprises as active principles at least one synthetic estrogenic compound and at least one progestogenic compound.

3. Medication or pharmaceutical composition according to the claims 1 and 2, characterized in that said medication or pharmaceutical composition contains

(a) about 0.001 to about 0.1 parts by weight of at least one estrogenic compound and

(b) about 0.1 to about 2.0 parts by weight of at least one progestogenic compound.

4. Medication of pharmaceutical composition according to any one of the claims 1 to 3, wherein the

ingredient (a) contains ethinyl estradiol and ingredient (b) contains norethindrone acetate.

5. Medication or pharmaceutical composition according to any one of the claims 1 to 4 for the treatment of estrogen deficiency.

6. Medication or pharmaceutical composition according to any one of the claims 1 to 5, packed as a solid dosage form in a pill case or compact for sequential administration.

7. A method of use of a combination of at least one estrogenic compound and at least one progestogenic compound for the manufacture of a medication or a pharmaceutical composition as claimed in any one of the claims 1 - 6.

8. A method of use according to claim 7 for the manufacture of a medication or a pharmaceutical composition for the treatment of estrogen deficiency, especially for the treatment of osteoporosis.

9. A process for the treatment of osteoporosis comprising administering to a patient a medication of pharmaceutical composition as claimed in any one of the claims 1 to 6.

10. A method of preparation of a medication or a pharmaceutical preparation as claimed in any one of the claims 1 to 6, characterized in that at least one estrogenic compound and at least one progestogenic compound are synergistically combined into a medication or a pharmaceutical preparation as claimed in any one of the claims 1 to 6.

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EUROPEAN SEARCH REPORT

Application number

EP 87 81 0103

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.4)
X	DICTIONNAIRE VIDAL, 1978, page 1639, O.V.P., Paris, FR; "Primodos" * Page 1639, "Primodos" * ---	1-10	A 61 K 31/57
X	DICTIONNAIRE VIDAL, 1970, page 912, O.V.P., Paris, FR; "Milli-anovlar" * Page 912, "Milli-anovlar * ---	1-10	
X	DICTIONNAIRE VIDAL, 1973, page 746, O.V.P., Paris, FR; "Gynovlane" * Page 746, "Gynovlane" * -----	1-10	

TECHNICAL FIELDS SEARCHED (Int. Cl.4)

A 61 K

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
THE HAGUE	16-06-1987	PEETERS J.C.

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
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